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HEMATOLOGIC NEOPLASIA LECTURE III
NON-HODGKIN MALIGNANT LYMPHOMAS

I. DEFINITION: Solid masses of neoplastic invasive lymphocytes with characteristics of B cells or T cells in various stages of gene rearrangement and phenotypic differentiation. These may be located in the LN or other peripheral tissues. Hodgkin's disease also involves neoplastic B cells or T cells but is separately classified..

II. CHARACTERISTICS OF NEOPLASTIC CLONES:

A. Genotype / Phenotype:

1. B-cell clones: Southern blot rearrangement of H-chain gene. Surface maturation antigens may be detected. Some produce cell-associated Ig (cIg or sIg) with unique idiotype (= Ig antigenic determinants). clones are classified by cytologic criteria of cell size,"cleaved" or "non-cleaved" nuclei) and by phenotypic expression of CD antigens
2. T-cell clones: Southern blot rearrangement of the genes for TCR-chain nuclei usually are folded, lobulated or convoluted

B. Sites of growth

1. B-cells: LN cortex, mucosa-associated lymphoid tissue (MALT) or other extranodal sites.
2. T-cells: LN paracortex, mediastinal remnants of pre-adolescent thymus

III. EXPERT SYSTEM OF HISTOPATHOLOGIC CLASSIFICATION

A. Classical histopathology: before the 1980s classification was based upon lymphocyte morphology and growth patterns: **follicular growth indicates cells of germinal center (B cell) origin and prognosis is better than with a diffuse growth pattern.**

B. World Health Organization: Working Formulation

1. low-grade = indolent lymphomas: small cells, few mitoses = slow growth -- **natural survival often > 5 years, life can be extended by supportive therapy, cure is not likely, BM transplant rarely succeeds.**

2. intermediate to high-grade lymphomas: large cells, many mitoses = rapid growth; diffuse growth pattern. **Natural survival is often < 2 years, but can respond well to aggressive chemotherapy and BM transplant is often successful.**

C. REAL classification.

integrates morphology, immunophenotype and molecular genetics with prognosis and response to therapy

IV. STAGING OF LYMPHOMAS: both for NON-HODGKIN & HODGKIN'S

A. Rationale: oncologists & radiotherapists place a major reliance on the extent of anatomic spread in selection of chemotherapy, immunotherapy, radiotherapy or BM transplantation

1. The extent of anatomic spread is described as stage I - IV: it is vigorously evaluated with an indicated combination of flat films, tomograms, CT scans, lymphangiograms and visceral or bone marrow biopsies
2. Clinical symptomatology:: A = none, B = fever, night sweats, excessive weight loss

B. Prognostic and therapeutic significance

1. Stage I or II = localized disease

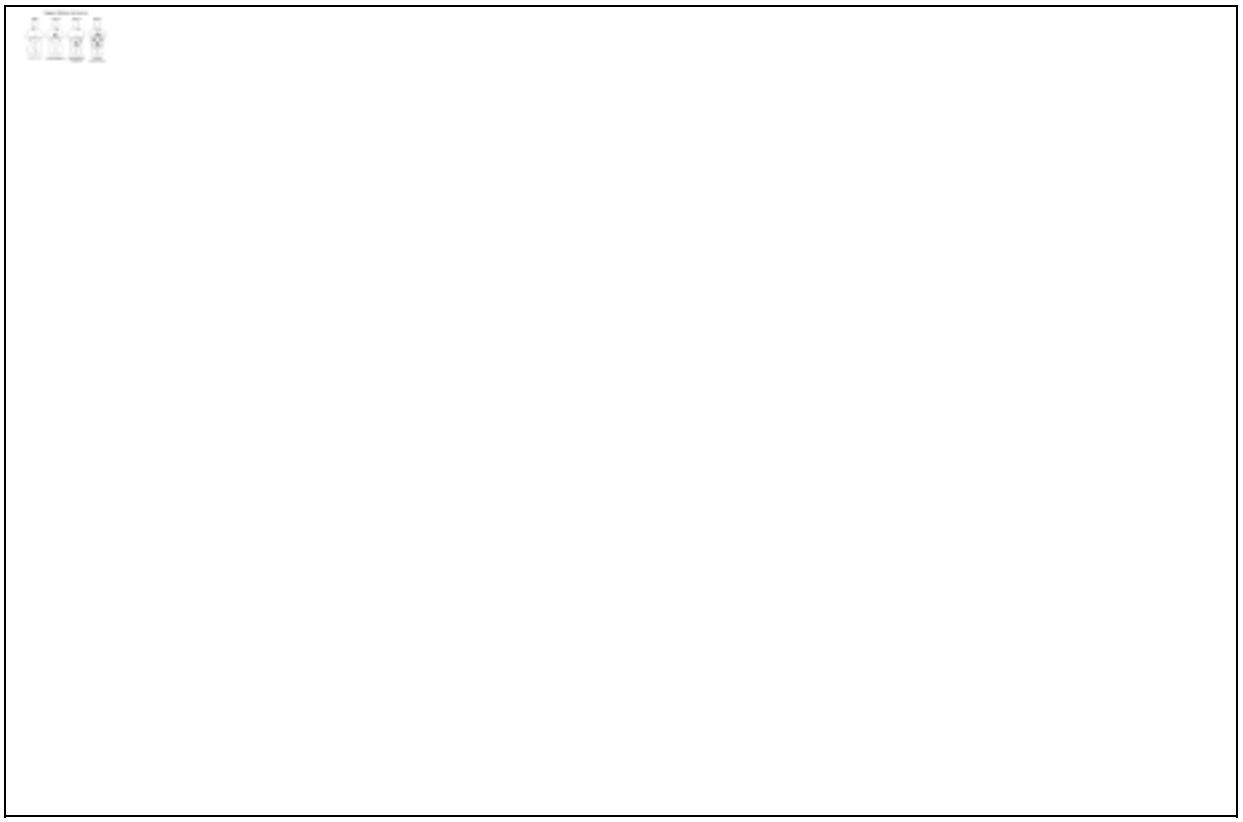
+ *low grade* = long survival, remissions with supportive chemotherapy

+ *high grade* = responsive to aggressive chemo- or radiotherapy, some cures, autologous BM transplants are often successful

2. bulky stage II or higher stage

+ *low grade* = moderate survival with supportive chemotherapy, few cures

+ *high grade* = possibly responsive to aggressive chemotherapy, but prognosis is guarded, matched BM transplants are sometimes successful



V. OTHER PROGNOSTIC FACTORS

A. Genetic abnormalities: significance is type-dependent, p53 mutation indicates a worse prognosis

B. Tumor bulk: increased LDH indicative of large mass and necrosis

VI. IMPORTANT EXAMPLES OF NON-HODGKIN LYMPHOMA (NHL)

B-cell tumors

A. Small Lymphocytic Lymphoma (SLL) = solid tumor cognate
1. Incidence: 7 % of all NHL in USA, median 60 y/o, rare under 40 y/o, male predominance
2. Clinical presentation: generalized lymphadenopathy
3. Stage: 90% @ stage III-IV, most with BM involved
4. Histopathology: diffuse LN replacement by mature B-cells
same phenotype found in CLL (see above) = low grade
5. Course & Prognosis: similar to CLL (trisomy 12 = poor prognosis)

B. Follicular Lymphomas –
1. Incidence: 30-50% of all NHL, median 55 y/o, rare < 40 y/o
2. Clinical presentation:painless lymphadenopathy,splenomegaly
3. Stage: 80% @ stage III-IV (50% with BM involved)
4. Histopathology germinal center origin, **follicular growth pattern, low grade, small cells with cleaved nuclear contours**
follicular center B cell phenotype: CD10, CD19, CD20

5. Pathogenesis: t(14;18) juxtaposes the *IgH* locus on 14 and the bcl-2 gene on 18
the antiapoptotic protein bcl-2 is overexpressed; cells fail to die and therefore accumulate abnormally

6. Course & Prognosis: indolent for up to 10 yr, need supportive chemotherapy during intervals of mild leukemic phases, eventually transform to higher grade diffuse large B cell lymphoma

C. Diffuse Large B Cell Lymphoma -there are several clinicopathologic subtypes
1. Incidence: median ~ 55 y/o, currently increasing in children and young adults, now maybe > 40% of all NHL
2. Clinical presentation: depends upon anatomic location, typically associated with an acquired immunodefiency
3. Stage: > 50 % present in stage III-IV BM involved in ~ 1/3 cases
in 50% GI tract primary
brain primary occur in transplant recipients, AIDS

4. Histopathology: diffuse growth with LN effacement, focal tissue necrosis & fibrous reaction mature B cells express CD19, 20 --- enlarge up to 5 X normal, prominent nucleoli
most are WHO intermediate grade
if huge cells with plasmacytoid features = high grade *immunoblastic*

5. Pathogenesis: EBV driven proliferation of B cells in setting of immunodeficiency. HSV8 infection in patients with advanced HIV-1 = body cavity lymphoma

In 30% of cases there is a translocation of the *BCL6* gene on chromosome 3
BCL6 is a transcription factor engaged in regulation of proliferation / differentiation
cases with t(14,18) and BCL-2 overexpression probably arise from a pre-esisting follicular lymphoma

6. Course & Prognosis: aggressive rapid growth, yet often responds to intensive combination chemotherapy with prolonged remissions. Bulky tumor and high LDH indicate poor prognosis

D. Burkitt Lymphomas -endemic and sporadic forms

1. Incidence: endemic in children of equatorial Africa
sporadic type represents ~ 30% of childhood NHL in USA , also seen in young adults

2. Clinical presentation:
   a. endemic: primary jaw and gonadal tumors predominate
   b. sporadic: primary locations in GI tract, BM, skeletal muscles

3. Stage: usually III or IV with BM involvement

4. Histopathology: diffuse growth, small non-cleaved B cells with multiple nucleoli, a very high N/C ratio and high mitotic index = high WHO grade. Cells express CD19, CD20 and are counterparts of immature germinal center cells. Interspersed pale macrophages produce a "starry sky" pattern and contain ingested tingible bodies representing nuclear debris of tumor cells undergoing spontaneous apoptosis (see Robbins Fig. 15-16)

5. Pathogenesis: EBV driven B-cell proliferation is followed by chromosomal translocation

t(8;14) and overexpression of *c-myc* Co-stimulation of B cells by malarial infection postulated to be the endemic factor in Africa. in Europe and the USA sporadic cases now represent a complication of HIV-1 infection or iatrogenic post-transplantation.

6. Course & Prognosis: Endemic cases sometimes respond well to aggressive chemotherapy
Sporadic cases often fare poorly, may need BM transplant

E. Mantle Cell Lymphoma

1. Incidence: 3 % of NHL in USA, up to 9% in Europe (Italy), median ~ 64 y/o, CD19,20,22 CD5
2. Clinical presentation: lymphadenopathy, fatigue
3. Stage: most with BM involved (stage IV), up to 40% with mild leukemic phase
4. Histopathology: the follicular mantle zone is expanded by a CD5+ clone of cleaved B cells. Derive from subset involved in primary immune response. Expresses IgM with L chain of a single isotype. Low to intermediate WHO grade.
5. Pathogenesis: **t(11;14) juxtaposes the *BCL1 (PRAD1)* locus with the gene for cyclin D1 on chromosome 11 to an H-chain locus on chromosome 14. Overexpression of cyclin D1 short circuits the G_1 checkpoint and deregulates progression through the cell cycle. Increase cyclin D1 detected**
6. Course & prognosis: Survival is 3-4 years. Therapy must be aggressive.

F. Extranodal Marginal Zone Lymphomas - nodal or extranodal
Mucosa Associate Lymphoid Tumors (MALT) = extranodal group

1. Incidence /clinical presentation: arise in adults with chronic enteritis or gastritis and other local auto-immune diseases
2. Stage: local organ growth at onset, may be reversible during oligoclonal phase
3. Histopathology: Often a follicular pattern consistent with germinal center origin. Immunophenotype variable:CD19, CD20, CD21. Sometimes referred to as monocytoid B cells (CD35+)
4. Pathogenesis and prognosis: **In GI tract may be initiated by *helicobacter pylori* infection may respond to a high dose antibiotic regimen.**

G. Post-transplant lymphoproliferative disorder:
1. Incidence /clinical presentation: occur in children who have received BM alllotransplants.
2. Stage: multifocal vascular or BM growth at onset
3. Histopathology: Nodular B-cell proliferations of donor origin
4. Pathogenesis and prognosis: post-transplant immunosuppression permits donor cell proliferation. Latent period up to years after a transplant, survival time often < 1 yr.

T-*cell tumors*

H. Precuror T-cell Leukemia/Lymphoma-precursor T cell cognate of T cell ALL
1. Incidence: ~ 5% of NHL, typically < 20 y/o
~ 40% of the NHL in children, adolescents & young adults
2 Clinical presentation: mediastinal mass in 50-70%
3. Stage: 75% present at stage III-IV, PB often involved
4. Histopathology: T-cells with convoluted nuclei and blastic features replace BM and LN TdT + immature T cells with CD1 or CD2, may co-express other T cell markers including both CD4 (T helper) and CD8 (T-suppressor cell antigen)
5. Molecular genetics: rearranged genes for T cell receptor chain

6. Pathogenesis: location suggests origin in the developing thymus
effusions may occur
Airway compression or strangulation of superior vena cava (SVC syndrome) is fatal.

I. Adult T-cell Lymphoma / Leukemia -a transmissible disease
1. Incidence: endemic to Carribean, Japan, New Guinea, India, Africa
sporadic in the USA,
2. rare disease of young adults to mid-life
3. Clinical presentation / Stage: may have cutaneous lesions or lytic bone lesions with complication of hypercalcemia (stage: III-IV)
4. Histopathology: leukemia or diffuse lymphoma, lymphocytes with multilobular nuclei
CD4+ T helper cells express IL-2 receptors
5. Pathogenesis: **the HTLV1 retrovirus -*oncovirus* is cell-associated and tropic for CD4 cells. It can be transmitted sexually, by transfusion or needle, or vertically by leukocytes in mother's milk. Donor blood must be screened to exclude seropositive**
6. Course and prognosis: usually fatal within months.

J. Mycosis Fungoides and Sezary Syndrome -a spectrum of cutaneous T-cell lymphomas
1. Incidence: rare disease, usual age > 40 yr,
2. Clinical presentation: skin inflammation with plaques or tumor nodules
3. Histopathology: atypical lymphocytes collect in the superficial dermis and invade the epidermis to form microabscesses
CD4 + cells with hyper-convoluted "cerebriform" nuclei
4. Pathogenesis: often a history of drug reaction or antecedent contact dermatitis HTLV-1 has been implicated but not proven
5. Course / Prognosis: chronic disease but difficult to control
treated with UV radiation, X-radiation of systemic chemotherapy some develop a leukemic phase with exfoliative dermatitis = *Sezary syndrome*